Larney, S., Tran, L. T., Leung, J., Santo Jr, T., Santomauro, D., Hickman, M., Peacock, A., Stockings, E., & Degenhardt, L. (2019). All-Cause and Cause-Specific Mortality Among People Using Extramedical Opioids: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, E1-E10. [4170]. https://doi.org/10.1001/jamapsychiatry.2019.4170

All-cause and cause-specific mortality in people using extra-medical opioids: A systematic review and meta-analysis

Sarah Larney PhD[1,2], Lucy Thi Tran BPsychSc (Hons)[1], Janni Leung PhD[3,4], Thomas Santo, Jr. MPH[1], Damian Santomauro PhD[4,5,6], Matt Hickman PhD[7], Amy Peacock PhD[1], Emily Stockings PhD[1], Louisa Degenhardt PhD[1]

[1]National Drug and Alcohol Research Centre, UNSW Sydney

[2]Alpert Medical School, Brown University

[3]School of Psychology, University of Queensland

[4]Institute of Health Metrics and Evaluation, University of Washington

[5]School of Public Health, University of Queensland

[6]Queensland Centre for Mental Health Research

[7]Population Health Sciences, Bristol Medical School, University of Bristol

Corresponding author:

Sarah Larney

National Drug and Alcohol Research Centre

University of NSW, Sydney NSW 2052

Australia

+61 478 555 405

s.larney@unsw.edu.au

Revision date: 28 October 2019

Word count: 3,500

Key points

Question: What are the mortality rates and key causes of excess mortality in people who use extra-medical opioids?

Findings: In this systematic review, people using extra-medical opioids died at ten times the rate of those of the same age and sex. Excess mortality occurs across traumatic causes of death, infectious diseases and non-communicable diseases.

Meaning: Responses to elevated mortality in people using extra-medical must include overdose prevention, but also incorporate interventions to prevent and treat infectious diseases and non-communicable diseases.

Abstract

Importance: Extra-medical opioid use has escalated in recent years. A better understanding of cause-specific mortality in this population is needed to inform comprehensive responses.

Objective: Estimate all-cause and cause-specific crude mortality rates (CMR) and standardised mortality ratios (SMR) among people using extra-medical opioids, including age- and sex-specific estimates where possible.

Data sources: Pubmed, PsycInfo and Embase were searched for studies published 2009-2018, and an earlier systematic review on this topic, published 2011.

Study selection: We included cohort studies of people using extra-medical opioids and reporting mortality outcomes. Studies were screened for inclusion independently by two team members. We included 1242~~26~~/8,~~602~~ 683 studies (10097~~7~~ primary studies and 240 studies providing additional data for primary studies).

Data extraction and synthesis: Data were extracted by one team member and checked by another. Study quality was assessed using a custom set of items that examined risk of bias and quality of reporting. Data were pooled using random-effects meta-analysis models in STATA 15.1. Heterogeneity was assessed using stratified meta-analyses and meta-regression.

Main outcomes and measures: All-cause and cause-specific CMRs and SMRs. The SMR measures the extent to which mortality is elevated relative to the general population of the same age and sex.

Results: The pooled all-cause CMR, based on 9~~7~~ cohorts including 1,262,592 people, was 1.~~6~~7 per 100 person-years (py; 95% confidence interval (CI) 1.~~4~~5, 1.~~8~~9), with substantial heterogeneity (I^2=99.7%). Heterogeneity was associated with the proportion of the study sample that injected opioids or was living with HIV or hepatitis C. The pooled all-cause SMR, based on 4~~3~~2 cohorts, was 10.0~~9.9~~ (95% CI 7.~~6~~5, 13.2~~1~~). Excess mortality was observed across a range of causes, including overdose, injuries, and infectious and non-communicable diseases.

Conclusions and relevance: People using extra-medical opioids experience significant excess mortality, much of which is preventable. The range of causes for which excess mortality was observed highlights the multiplicity of risk exposures experienced by this population, and the need for comprehensive responses that address these. There remains a need for better data on cause-specific mortality in this population in several world regions. PROSPERO registration CRD421018094623.

Extra-medical opioid use includes the use of heroin and other illicitly manufactured opioids, as well as ~~the~~ use of pharmaceutical opioids outside the bounds of a medical prescription.[1] It is a significant public health problem ~~in many countries globally~~,[2] with use and related harms escalating across many high income countries.[3] In the United States, HIV and hepatitis C virus (HCV) outbreaks associated with opioid injecting have been observed,[4,5] and fatal opioid overdoses have increased dramatically, exceeding 47,000 deaths in 2018.[6] Increa~~sing trends se~~d~~in~~ fatal opioid overdoses have also been observed in Canada, ~~the~~ United Kingdom, Australia, and Europe.[7-10]

Overdose is not the only risk of extra-medical opioid use and injecting. In a previous systematic review, AIDS-related causes were at least as common as overdose deaths in six of 25 cohorts reporting both causes of death.[11] More recently, increasing rates of HCV-related deaths have been observed in cohorts of people with a history of opioid dependence.[12] Other elevated causes of death include suicide and other injuries.[11]

Given the dynamic nature of extra-medical opioid use and related deaths, it is timely to review data on mortality ~~rates and excess mortality~~ among people who use extra-medical opioids, particularly cause-specific mortality. ~~There is a need for data on cause-specific excess mortality to shed light on both overdose and non-overdose deaths in this population.~~ We aimed to ~~systematically review the literature to~~ estimate all-cause and cause-specific crude mortality rates, standardised mortality ratios, and relative risks, with sex- and age-specific estimates where possible.

Method

Reporting of this review is in line with the MOOSE guidelines.[13] The review protocol was registered with PROSPERO (registration number CRD42018094623).

Search strategy and study selection

A previous systematic review on this topic[11] was used to identify studies published from 1980 to 2008. Medline, Embase and PsycINFO databases were searched using the OVID interface/platform to identify relevant articles published from January 2009 until February 2018. ~~An updated search was conducted to identify any recent relevant publications until~~Searches were updated in October 2019. Search strings ~~incorporating keywords and Medical Subject Headings (MeSH terms) reflecting drug type and mortality epidemiology were used and~~ are provided ~~in full~~ in Appendix 1. No language restrictions were applied to the search, with the research team able to read in English, Italian, French, and Chinese. Studies in languages other than these were read using Google Translate.

Study selection was completed using Covidence~~, a web-based systematic review management tool~~ (https://www.covidence.org). Team members were trained in the requirements for inclusion of a study. Each retrieved citation was screened for inclusion based on title and abstract. All publications marked as excluded at this stage were reviewed by a second person and if there was a difference in the assessment, the publication was included for the next stage of the review ~~All publications marked as excluded at this stage were reviewed by a second person who could overturn the initial exclusion decision~~. Each study included after initial screening was reviewed in full ~~independently~~ by two people. Disagreements were resolved through discussion between the two reviewers and referral to a third party if needed. Reference lists of reviews ~~that were~~ identified by the search were ~~also~~ screened to identify any additional publications.

Inclusion and exclusion criteria

We included cohort studies of people who use extra-medical opioids, recruited in any setting, that reported data on crude mortality rates (CMRs) and/or standardised mortality ratios (SMRs). This

could include cohort studies of people who inject drugs, provided at least 90% of the cohort reported extra-medical opioid use. Cohorts did not need to be opioid dependent or have opioid use disorder to be included. Cohorts of people prescribed opioids for pain management or were exclusively people living with HIV or HCV were excluded, as were studies that reported case fatality rates only. Full inclusion and exclusion criteria are described in Appendix 2.

Data extraction

Data were extracted into a spreadsheet by one member of the research team and checked by anothera second member of the team. Extracted variables included study information (e.g. study country, years of data collection) and sample information (e.g. sex distribution, mean or median age, HIV and HCV status of participants) considered *a priori* to be potentially relevant to between-study heterogeneity. We extracted number of observed deaths, person-years of follow-up, and expected deaths to allow for calculation of CMRs and SMRs, but alsoand extracted CMRs and SMRs as reported. Specific causes for which data were extracted were overdose, AIDS-related, suicide, accidental injuries, homicide, liver disease, cardiovascular disease, respiratory disease, and cancer. When data for a study were incomplete, authors were contacted by email for additional information.

During data extraction, it became apparent that there were inconsistencies were identified between studies in how overdose deaths were defined. Some studies stated only that they reported overdose mortality rates without explaining how overdose was defined. Where definitions were reported (typically using International Classification of Disease (ICD)-9 or ICD-10 codes), the most restrictive definitions included only opioid poisoning (n=6), while others included opioid and otherany drug poisoning (n=27). Less restrictive definitions included poisoning deaths as well as deaths attributed to mental and behavioural disorders due to psychoactive substance use (n=29). Pooled estimates were therefore calculated separately for the followingthree definitions of overdose death: opioid poisoning; poisoning due to any drug (including alcohol if it was not possible to disaggregate by

drug); and poisoning due to any drug and mental and behavioural disorders due to psychoactive substance use. Differences were also observed in how liver diseases were coded. We calculated pooled estimates for the following definitions: viral hepatitis (n=7); digestive diseases (including codes 520-579 in ICD-9 or Chapter XI of ICD-10; n=11); and liver-related (which typically included both of the previous categories, plus liver cancer; n=20).

Study quality, including risk of bias

As risk of bias tools for observational epidemiological studies are still evolving~~.~~,[14] we developed a review-specific tool with ~~close~~ reference to two recent publications on assessing risk of bias in observational studies of exposures.[14,15] The tool assessed each study on two risk of bias domains and three quality of reporting domains (Appendix 3). Risk of bias domains were sample representativeness and outcome measurement. Studies were rated as being at higher or lower risk of bias on each of these domains. Quality of reporting domains were completeness of reporting of cohort characteristics, completeness of outcome data, and reporting of definitions used for cause-specific deaths. Studies were assessed as having higher or lower quality reporting on each of these domains. ~~This information was used to add context regarding the validity of the findings.~~

Data analysis

CMRs were calculated as deaths per 100 person-years, and SMRs as observed deaths over expected deaths. We derived 95% confidence intervals for each metric using standard formulas (see Appendix 4).

SMRs represent the ratio of mortality risk among those exposed to the risk and the entire population, including those exposed to the risk. Relative risks (RRs) illustrate the ratio of mortality risk between those exposed to the risk and those not exposed to the risk. With a low prevalence exposure such as extra-medical opioid use, SMRs and RRs should be similar. We estimated RRs from SMRs by adjusting the SMR by the proportion of the general population that is exposed to the risk.[16] Data on general population risk exposure were obtained from the Global Health Data Exchange.[17]

We explored heterogeneity through stratification and meta-regression and used random effects models for pooling data as we expected that there would be variation between the samples selected by the studies. For pooled analyses, w~~W~~e used ~~used Stata 15.1 to complete~~ DerSimonian and Laird ~~Mantel-Haenszel~~ random-effects meta-analyses in Stata 15.1. Study weights incorporated both within- and between-study error. ~~to determine pooled all-cause and cause-specific CMR and SMR estimates. Random effects models were selected as we expected high levels of heterogeneity between cohorts.~~ Heterogeneity was quantified using the I^2 statistic. We took I^2 of ≤25%, 25-≤50%, and >50% to indicate low, moderate and substantial heterogeneity, respectively.[18]

~~We explored heterogeneity in the all-cause CMR and SMR through stratified meta-analyses and meta-regressions.~~ Stratification variables for exploring heterogeneity included sex, age groups, year ~~of completion of~~ follow-up completion (with 1994 selected as the cut-point due to the introduction of highly active antiretroviral therapy for HIV in that year), injecting drug use ~~status~~, opioid dependence/use disorder, recruitment setting (drug treatment or harm reduction settings compared to all other settings), and geographic region as defined by the Global Burden of Disease study. Depending on how data were presented, age groups were defined as <30 years compared to ≥30 years, or <35 years compared to ≥35 years, and hereafter referred to as younger (<30 years and <35 years pooled) compared to older (≥30 years and ≥35 years pooled). ~~To increase the specificity of stratified estimates,~~ A~~a~~ll-cause and cause-specific CMR ratios comparing men and women, and younger and older people, were estimated.

Each meta-regression included a single moderator variable, which could be a feature of the study sample (e.g. ~~sex ratio;~~ HIV prevalence) or a feature of the study design or conduct (e.g. ~~sample size;~~ recruitment setting). Variables were only included in meta-regressions if 5 or more data points were available. We took p<.05 to indicate an explanatory moderator variable that influenced heterogeneity in the CMR or SMR.

Distribution of causes of death

~~Finally, we~~To examine~~d~~ the distribution of causes of death across cohorts, ~~,~~ w~~W~~e identified the subset of cohorts where a cause was specified for all observed deaths (including that cause for *x* deaths was undetermined, as opposed to not reported ~~or missing~~), and grouped deaths into the following categories: poisoning/substance dependence, infectious diseases, non-communicable diseases, trauma, and undetermined. In keeping with ~~the way that cause-specific deaths were classified~~classifications used in the included studies, deaths attributed to viral hepatitis were included in infectious diseases, but deaths attributed to liver disease were included in non-communicable diseases, despite likely being sequelae of viral hepatitis infection. The weighted mean of the proportion of deaths in the cohorts due to each category was calculated, along with 95% confidence intervals based on a t distribution. Data on certain subordinate causes within a category were commonly reported, including AIDS-related deaths within infectious diseases; cancer and liver disease within non-communicable diseases; and suicide within trauma. Weighted means of the proportion of deaths within the cohorts due to these causes were also calculated.

Results

The PRISMA study flow diagram is shown in Figure 1. We included 124~~117~~ publications, including 100~~97~~ primary publications and 2~~40~~ secondary publications providing additional data for these primary publications. Cohorts were recruited from 28 countries, including 5 low- and middle-income countries (9 studies). Cohort size ranged from 100~~35~~ to 306,786 people and person-years of follow-up ranged from 129 to 687,673. Characteristics of included studies are provided in Appendix 5.

Risk of bias and study quality

Just under half (43%) of the included cohorts were rated as being at higher risk of bias in relation to cohort representativeness (e.g. were recruited from a single site), and one quarter (24%) were at higher risk of bias relating to outcome measurement (e.g. mortality data derived from clinical records rather than death registries). Only 9% of cohorts did not report age and sex data to characterise the cohort sample. Just over a quarter (27%) of cohorts reported incomplete mortality data (i.e. missing either numerator or denominator), and 42% of the 80 cohorts reporting cause-specific mortality did not report the definitions used to categorise deaths. A summary table and individual study assessments are provided in Appendix 6.

All-cause mortality

The pooled all-cause CMR, based on 9~~7~~ cohorts, was 1.6~~7~~ per 100 py (95% CI: 1.4~~5~~, 1.8~~9~~), with substantial heterogeneity (99.7%) (Table 1). Forest plots for this and all following pooled analyses are provided in Appendix 7. The highest CMRs were observed in South Asia (7.6 per 100 py; 95% CI: 4.8, 12.0; 2 cohorts, both from Bangladesh) and the lowest in Australasia (0.8 per 100 py; 95% CI: 0.7, 1.0; 7 cohorts, all from Australia) (Table 1).

In cohorts of people who injected opioids, the pooled all-cause CMR was 2.7 per 100 py (95% CI: 2.1, 3.4) (Table 1). The prevalence of injecting drug use, HIV infection, and HCV infection within study samples were all important sources of heterogeneity and positively associated with higher CMRs (Table 2). Crude mortality rates were higher among men compared to women (CMR ratio 1.4, 95%

CI: 1.3, 1.5), and among younger people compared to older people (CMR ratio 2.01.9, 95% CI: 1.65, 2.53) (Table 3).

The pooled all-cause SMR, based on 432 cohorts, was 10.09.9 (95% CI: 7.65, 13.21), with substantial heterogeneity (99.9%) (Table 1); among cohorts of people injecting opioids, the pooled all-cause SMR was 16.4 (95% CI: 10.9, 24.6) (Table 1). The highest pooled SMR was observed in Southeast Asia (13.4; 95% CI: 11.4, 15.3), and the lowest in North America (5.0; 95% CI: 4.2, 6.0). Excess mortality was more pronounced among women compared to men, and in younger people relative to older people (Table 3). Only the proportion of the cohort that injected drugs showed strong evidence of positive association with greater excess mortality (Table 2).

Drug-related deaths

There were 563 cohorts presenting data on drug-related deaths (Table 3). Across the three definitions for which data were extracted, the pooled CMR was 0.5 per 100 py (95% CI: 0.5, 0.6). Men had significantly higher drug-related mortality rates than women, as did older people relative to younger people (Table 3). Drug-related death was substantially elevated relative to the population (SMR 58.4; 95% CI: 38.1, 89.6) (Table 43 and Appendices 7 and 8). ~~Women and older people had higher drug-related SMRs than men and older people (Table 4 and Appendix 7).~~

Traumatic deaths: Suicide, accidental injuries, and homicide

Suicide and accidental injury deaths occurred at similar rates (pooled CMR for suicides and accidental injuries 0.1 per 100 py; 95% CI: 0.1, 0.2). ~~The pooled CMR for suicide deaths was 0.1 per 100 py (95% CI: 0.1, 0.2) (Table 3). Suicide deaths were more common among men than women (Table 3; pooled CMR ratio 1.87; 95% CI: 1.4, 2.2), and older people than younger people (Table 3; pooled CMR ratio 1.64; 95% CI: 1.1, 2.21.7).~~ Suicide deaths occurred at almost ~~more than~~ 8 times the expected rate (~~Table 4;~~ pooled SMR 7.98.5; 95% CI: 5.76.0, 11.012.1), and accidental injuries, seven times the expected rate (pooled SMR 6.9; 95% CI: 4.4, 10.6) Table 3). Death from interpersonal

violence was a relatively infrequent cause of death (pooled CMR 0.03 per 100 py; 95% CI: 0.02, 0.03) (Table 3), but occurred at more than 9 times the expected rate (pooled SMR 9.8; 95% CI: 6.6, 14.4) (Table 3).

~~Accidental injury deaths occurred at a similar rate to suicides (Table 3; pooled CMR 0.1 per 100 py; 95% CI: 0.1, 0.2), and were more common among men than women (Table 3; pooled CMR ratio 1.8; 95% CI: 1.6, 2.1). The pooled accidental injury SMR was 6.9 (95% CI: 4.4, 10.6) (Table 4).~~

~~Death from interpersonal violence was a relatively infrequent cause of death (pooled CMR 0.03 per 100 py; 95% CI: 0.02, 0.03) (Table 3), but occurred at more than 9 times the expected rate (pooled SMR 9.8; 95% CI: 6.6, 14.4) (Table 4).~~

AIDS-related deaths

The pooled CMR for AIDS-related deaths was 0.2 per 100 py (95% CI 0.1, 0.3) (Table 3), and the pooled SMR was 18.5 (95% CI 8.2, 42.0) (Table 43). Excess mortality due to AIDS was particularly pronounced among women (pooled SMR 54.03~~.98~~; 95% CI 21.62~~2~~, 134.73~~3~~; Appendix 8).

Liver-related deaths

The overall CMR was 0.12~~2~~ per 100 py (95% CI 0.1, 0.3) (Table 3), and liver-related deaths were more common among men relative to women (Table 3; pooled CMR ratio 1.7; 95% CI: 1.4, 2.1) and older people relative to younger people (Table 3; pooled CMR ratio 7.7, 95% CI: 5.8, 10.0). Liver-related deaths occurred at ~~more than~~ 8 times the expected rate (Table 43; pooled SMR 8.0~~6~~, 95% CI: 6.5~~1~~, 9.912~~.1~~).

Other disease deaths: Cardiovascular disease, cancer, and respiratory disease

~~Studies reported mortality rates due to a range of non-communicable diseases, most commonly,~~Pooled CMRs were similar for cardiovascular disease (pooled CMR 0.1 per 100 py; 95% CI: 0.1, 0.2), cancer (pooled CMR 0.1 per 100 py; 95% CI: 0.1, 0.2), and respiratory disease (including chronic respiratory disease and acute infections; pooled CMR 0.1 per 100 py; 95% CI: 0.1, 0.1) (Table

3). SMRs were elevated across all of these causes, particularly respiratory disease (pooled SMR 10.6; 95% CI: 7.8, 14.4) (Table 43).

Relative risks

Relative risks of all-cause and cause-specific death were similar to the reported SMRs and are shown in Appendix 89.

Distribution of causes of death

There were 19 cohorts reporting a cause for all observed deaths that could be included in an the analysis of distribution of causes of death, mostly originating from Western Europe (see Appendix 9 10 for included cohorts). Poisoning/substance-related (including alcohol-related) deaths were the most common cause, accounting for just under one-third of deaths (31.5%; 95% CI: 25.1%, 37.8%) (Figure 2). Non-communicable diseases accounted for one-quarter (24.1%; (95% CI: 17.1%, 31.2%) of deaths. Infectious diseases (19.7%; 95% CI: 11.7%, 27.8%) and traumatic deaths (18.1%; 95% CI: 12.6%, 23.7%) each accounted for nearly one in five deaths across these cohorts.

Discussion

~~Globally, people~~People who use extra-medical opioids ~~have~~ had an elevated risk of mortality across ~~several~~ major causes of deaths, including ~~cancer, cardiovascular disease and respiratory~~non-communicable diseases~~, as well as~~ overdose, infectious diseases, and injuries. Variation in mortality between cohorts was driven by the prevalence of injecting drug use, HIV, and HCV within study cohorts. Most cohorts were recruited from multiple sites or used population-based registries covering a broad geographic area, and mortality was typically ascertained using official death registries, contributing to confidence in the findings. Relative to a previous systematic review of this question,[11] we have highlighted the significant burden of mortality due to non-communicable diseases in this population, and provided sex- and age-specific estimates of cause-specific excess mortality. ~~This high level of mortality across multiple causes of death highlights the range of risk exposures experienced by this population. For example, a high prevalence of smoking and oncogenic viruses such as HCV contribute to cancer deaths nearly three times as high as expected.~~

Implications

Addressing this burden ~~of mortality~~ requires a range of strategies to address different risk exposures. Opioid agonist treatment (OAT) significantly reduces mortality across a range of causes, including drug-related deaths, suicides, and injuries, but is often not accessible for many people who could benefit from treatment, even in high-income countries.[19-21] In addition to reducing overdose and other mortality, ~~increasing access to~~ OAT ~~can~~ reduces HIV and HCV infections[22,23] and ~~criminal offending~~contact with the legal system,[24] ~~thereby~~ generating broad public health ~~and safety~~ benefits.

~~Although OAT is effective in reducing overdose, l~~Increased access to naloxone in the community is also required to enable acute management of overdoses. Take-home naloxone programs are effective in reducing mortality among program participants,[25] and emerging evidence suggests that widespread naloxone distribution may impact on population overdose mortality.[26]

~~Ongoing significant~~ E~~e~~xcess mortality due to HIV and viral hepatitis points to the need to increase access to treatment for HIV and HCV infections. People who use and inject drugs have poor access to HIV antiretroviral therapies in many countries, largely ~~as a result of~~due to socio-structural barriers such as policies or clinician preference to avoid treatment initiation in people who use drugs, and stigma and discrimination.[27,28] HCV infection is endemic in people who inject drugs~~, reflected in elevated liver-related deaths~~.[29] New highly effective, curative treatments for HCV infection should address this burden, but access to treatment is likely to remain an issue in many countries.[30]

Smoking is highly prevalent among people who use extra-medical opioids,[31] reflected here in excess mortality due to cardiovascular disease, respiratory disease, and cancer. Smoking cessation programs have been trialled in OAT settings, with nicotine replacement therapies being superior to placebo, and adjunctive behavioural therapies having no additional impact on abstinence at follow-up.[32] However, absolute rates of sustained smoking cessation are low.[33] There is a need to improve access to and effectiveness of smoking cessation interventions in this population.[33]

In terms of structural factors potentially associated with all-cause mortality, in meta-regression analyses neither homelessness nor past incarceration appeared to be important variables. However, there were few studies (n=7) reporting on homelessness in their samples, and extreme excess mortality across all causes has frequently been observed in people who are unsheltered,[34] with ~~overdose, suicide and other~~ unnatural deaths particularly increased relative to housed populations.[35] ~~Much of the work on homelessness and mortality has been undertaken with the wider population of people who are homeless.~~ In light of the current overdose crisis, there is a need for evidence on the role of housing in ~~mortality~~ overdose incidence and outcomes~~ specifically in people using extra-medical opioids, particularly associations between access to housing and overdose mortality rates~~. There were also few (n=14) studies reporting ~~-~~incarceration ~~history~~ in their samples, and incarceration was often defined in terms of lifetime exposure. Given that release from incarceration

increases overdose mortality risk,[36] better characterisation of recent incarceration is essential for better understanding its impact on mortality in this population.

Limitations of included studies

A key limitation ~~of included cohorts was missing~~was lack of information on how ~~specific~~ causes of death were defined. Of the 80 cohorts with cause-specific mortality rates, 34 did not report how specific causes were defined. Of those with definitions, there was significant variation between studies in defining drug- and opioid-related deaths. Consistency in defining drug- and opioid-related deaths is critical to ensuring accurate monitoring and assessing progress towards reducing drug-related deaths across and within countries. Liver-related deaths were another broad area where inconsistencies were identified. Clarification and increasing consistency of the codes included in this category would assist in enabling monitoring of ~~HCV elimination and~~the public health impacts of HCV antiviral therapies.

A previous systematic review on this topic ~~noted that~~identified very little data from low- and middle-income countries ~~had been identified~~.[11] There have been only minor increases in data from low- and middle-income countries in this review, and there remain several world regions (e.g. Latin America and the Caribbean, Sub-Saharan Africa) with no relevant data ~~on excess mortality in people using extra-medical opioids. Such data are needed to, for example, determine need for overdose prevention programs, and assess access to HIV antiretroviral therapy among people who use drugs.~~

Limitations of this review

Despite a comprehensive search strategy including reports in any language, it is possible we did not identify some cohorts. There were limited age- and sex-specific CMRs and SMRs for several key causes of death, which is a concern given changes in dominant causes of death across the lifespan for people using extra-medical opioids.[37] We did not seek to determine mortality rates in relation to engagement in OAT, as this work has recently been completed ~~recently by Sordo and colleagues~~.

~~Their~~ That review confirmed that OAT with either methadone or buprenorphine is highly protective against death, although there are periods of elevated mortality risk during methadone induction and after treatment cessation.[38] We were unable to explore heterogeneity in cause-specific deaths associated with country or region of origin due to small numbers of studies for most causes.

This review related specifically to people using, injecting, and/or seeking treatment for their use of extra-medical opioids such as heroin. ~~Our definition~~We did not exclude people with infrequent or non-disordered extra-medical opioid use, which may have contributed to heterogeneity in our estimates. However, the CMR limited to ~~cohorts defined as~~ opioid dependent cohorts was similar to the overall CMR, suggesting that this definition did not substantially impact on the results. Notwithstanding that in some settings there is considerable overlap between people using illicit opioids and people using extra-medical pharmaceutical opioids, we do not consider that the results presented here apply to people who are prescribed opioids and not engaging in extra-medical opioid use. ~~A separate review of mortality in that population reported a higher pooled all-cause CMR (2.4 per 100 py; 95% CI: 0.9, 6.2) relative to this study, likely due to the substantially older age profile of the included samples. The pooled overdose CMR in people prescribed opioids was low (0.06 per 100 py; 95% CI 0.02, 0.2).~~

Conclusions

People who use extra-medical opioids experience a high burden of excess mortality across a range of causes. Combinations of evidence-based interventions to reduce mortality will have significantly greater impact than single interventions.[39] Combinations of OAT, needle and syringe programmes, and naloxone as well as treatment for HIV and HCV infections will have synergistic impacts in reducing overdose, disease incidence, and mortality due to multiple adverse health outcomes. There is an urgent need to scale up combination interventions across myriad health issues to ensure that people who use opioids no longer face elevated mortality risks for health outcomes for which evidence-based interventions (such as nicotine replacement therapy for smoking cessation) are

easily available to the wider community. ~~These findings reinforce the need for widely available OAT; increased access to naloxone among people using opioids and their social networks; and increased access to HIV and HCV treatments and smoking cessation for this population.~~

Funding

No specific funding was received for this review. The National Drug and Alcohol Research Centre is supported by funding from the Australian Government Department of Health under the Drug and Alcohol Program. SL and LD are supported by Australian National Health and Medical Research Council Fellowships (GNT1140938 and GNT1135991) and NIH R01 DA044170. ES and AP are supported by Australian National Health and Medical Research Council Fellowships (GNT 1104600 and GNT1109366). DS is employed by the Queensland Centre for Mental Health Research which receives core funding from the Department of Health, Queensland Government. MH acknowledge support from NIHR Health Protection Research Unit (HPRU) in Evaluation of Interventions at University of Bristol. MH is an NIHR senior investigator and acknowledges NIHR School of Public Health Research. JL is supported by a Development Fellowship from the University of Queensland.

Conflicts of interest

SL has received untied educational grants for studies of opioid medications in Australia from Indivior. AP has received untied educational funding from Mundipharma and Seqirus for work unrelated to the current study (i.e., postmarketing surveillance of specific pharmaceutical opioid formulations). LD has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma and Seqirus. Dr. Hickman reports personal fees from Gilead, MSD, Abbvie. None of these funders had any knowledge of or were involved in this work.

SL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick RP. Definitions related to the use of pharmaceutical opioids: Extramedical use, diversion, non-adherence and abberant medication-related behaviours. *Drug and Alcohol Review* 2011; **30**: 236-45.
2. Degenhardt L, Charlson F, Ferrari A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Psychiatry* 2018; **5**(12): 987-1012.
3. OECD. Addressing problematic opioid use in OECD countries. Paris: OECD Health Policy Studies, 2019.
4. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years — Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *Morbidity and Mortality Weekly Report* 2015; **64**(17): 453-8.
5. Peters PJ, Pontones P, Hoover KW, et al. HIV infection linked to injection use of oxymorphone in Indiana, 2014-2015. *New England Journal of Medicine* 2016; **375**: 229-39.
6. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths - United States, 2013-2017. . *MMWR* 2019; **67**: 1419-27.
7. Roxburgh A, Hall WD, Dobbins T, et al. Trends in heroin and pharmaceutical opioid overdose deaths in Australia. *Drug and Alcohol Dependence* 2017; **179**: 291-8.
8. British Columbia Coroners Service. Illicit Drug Overdose Deaths in BC: Office of the Chief Coroner, 2017.
9. Office for National Statistics. Deaths related to drug poisoning in England and Wales: Office for National Statistics, 2017.
10. EMCDDA. European Drug Report. Lisbon: European Monitoring Centre on Drugs and Drug Addiction, 2018.
11. Degenhardt L, Bucello C, Mathers BM, et al. Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. *Addiction* 2011; **106**: 32-51.
12. Larney S, Randall D, Gibson A, Degenhardt L. The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people. *Drug and Alcohol Dependence* 2013; **131**: 252-7.
13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *Journal of the American Medical Association* 2000; **283**(15): 2008-12.
14. Bero L, Chartres N, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Systematic Reviews* 2018; **7**: 242.
15. Wang Z, Taylor K, Allman-Farinelli M, et al. A systematic review: Tools for assessing methodological quality of human observational studies. Canberra: National Health and Medical Research Council, 2019.
16. Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *American Journal of Epidemiology* 1998; **148**: 1012-7.
17. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle: Institute for Health Metrics and Evaluation, 2018.
18. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Review of Interventions Version 5.1.0. Available from www.cochrane-handbook.org: The Cochrane Collaboration; 2011.
19. Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health* 2015; **105**: e55-e63.
20. Abraham AJ, Adams GB, Bradford AC, Bradford WD. County-level access to opioid use disorder medications in medicare Part D (2010-2015). *Health Services Research* 2019; **54**(2): 390-8.

21. Larney S, Peacock A, Leung J, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: A systematic review. *Lancet Global Health* 2017; **5**: e1208-20.
22. Platt L, Minozzi S, Reed J, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. *Addiction* 2018; **113**: 545-63.
23. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: Systematic review and meta-analysis. *BMJ* 2012; **345**: e5945.
24. Gisev N, Bharat C, Larney S, et al. The effect of entry and retention in opioid substitution therapy on contact with the criminal justice system among opioid dependent people. *Lancet Public Health* 2019; **4**: e334-e42.
25. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction* 2016; **111**(7): 1177-87.
26. Bird S, McAuley A. Scotland's National Naloxone Programme. *The Lancet* 2019; **393**: 316-8.
27. UNAIDS. Health, rights and drugs: Harm reduction, decriminalization and zero discrimination for people who use drugs. Geneva: UNAIDS, 2019.
28. Parashar S, Collins AB, Montaner JSG, Hogg RS, Milloy MJ. Reducing rates of preventable HIV/AIDS-associated mortality among people living with HIV who inject drugs. *Current Opinion in HIV and AIDS* 2016; **11**(5): 507-13.
29. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: A multistage systematic review. *Lancet Global Health* 2017; **5**: e1192-207.
30. Day E, Hellard M, Treloar C, et al. Hepatitis C elimination among people who inject drugs: Challenges and recommendations for action within a health systems framework. *Liver International* 2019; **39**(1): 20-30.
31. Guydish J, Passalacqua E, Pagano A, et al. An international systematic review of smoking prevalence in addiction treatment. *Addiction* 2016; **111**: 220-30.
32. Yee A, Hoong MC, Joyce YC, Loh HS. Smoking cessation among methadone-maintained patients: A meta-analysis. *Substance Use and Misuse* 2018; **53**: 276-85.
33. de Dios MA, Cano MA, Vaughan EL, McNeel MM, Childress S, Niaura R. Nicotine maintenance for smokers in methadone treatment: A new direction. *Addiction Research and Theory* 2019; **27**: 269-76.
34. Aldridge RW, Story A, Hwang SW, et al. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: A systematic review and meta-analysis. *Lancet* 2018; **391**: 241-50.
35. Slockers MT, Nusselder WJ, Rietjens J, van Beeck EF. Unnatural death: A major but largely preventable cause of death among homeless people? . *European Journal of Public Health* 2018; **28**: 248-52.
36. Merrall ELC, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; **105**: 1545-54.
37. Degenhardt L, Larney S, Randall D, Burns L, Hall W. Causes of death in a cohort treated for opioid dependence between 1986 and 2005. *Addiction* 2014; **109**: 90-9.
38. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357**: j1550.
39. Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: Harms to populations, interventions, and future action. *The Lancet* 2019; **394**: 1560-79.
40. Apelt SM, Scherbaum N, Golz J, Backmund M, Soyka M. Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: Results from a nationwide non-interventional study in routine care. *Pharmacopsychiatry* 2013; **46**(3): 94-107.

41. Smyth BP, Fagan J, Kernan K. Outcome of heroin-dependent adolescents presenting for opiate substitution treatment. *Journal of Substance Abuse Treatment* 2012; **42**(1): 35-44.

Table 1: Pooled all-cause crude mortality rates among people using extra-medical opioids, by sex, age group, drug use characteristics, and region

	Crude mortality rates			Standardised mortality ratios		
Strata	**N cohorts**	**Pooled crude mortality rate per 100PY (95%CI)**	**I^2**	**N cohorts**	**Pooled standardised mortality ratio (95%CI)**	**I^2**
All-cause mortality	99[1]	1.59 (1.40-1.80)	99.7%	43	10.03 (7.64-13.17)	99.9%
Sex						
Men	47	1.85 (1.51-2.27)	99.7%	31	8.56 (6.70-10.93)	99.9%
Women	43	1.28 (1.03-1.58)	99.4%	30	13.40 (8.90-20.16)	99.9%
Age[2]						
Younger	18	1.25 (0.91-1.71)	99.5%	5	10.96 (4.59-26.16)	99.8%
Older	18	2.09 (1.51-2.91)	99.9%	5	5.24 (4.53-6.05)	94.6%
Follow up completed						
By end of 1994	7	1.85 (0.97-3.55)	99.8%	4	9.33 (4.98-17.46)	99.4%
Continued or commenced in 1995 or later	90	1.57 (1.39-1.78)	99.6%	39	10.10 (7.56-13.50)	99.9%
Injecting cohorts[3]	19	2.71 (2.14-3.42)	95.2%	10	16.37 (10.92-24.55)	98.8%
Dependent cohorts[4]	67	1.54 (1.33-1.78)	99.7%	36	10.31 (7.63-13.93)	99.9%
Recruitment setting						
Drug treatment or harm reduction setting	57	1.58 (1.37-1.82)	99.5%	29	10.25 (7.78-13.51)	99.8%
Other settings[5]	40	1.60 (1.31-1.96)	99.7%	14	9.42 (7.74-11.46)	99.5%
GBD region[6]						
Australasia	7	0.80 (0.67-0.96)	91.3%	3	8.63 (6.49-11.47)	93.2%
East Asia	6	1.80 (1.37-2.35)	96.7%	4	9.89 (6.15-15.92)	98.2%
Southeast Asia	3	4.53 (3.11-6.62)	69.3%	1	13.40 (11.40-15.30)	-
South Asia	2	7.62 (4.84-12.00)	60.9%	-	-	-
North Africa & Middle East	2	3.40 (0.97-11.87)	95.2%	-	-	-
Central Europe	3	1.17 (0.61-2.23)	96.2%	1	12.06 (9.60-15.00)	-
Western Europe	54	1.56 (1.32-1.84)	99.5%	27	11.87 (9.15-15.40)	99.8%
North America	20	1.61 (1.36-1.91)	99.5%	7	5.02 (4.21-5.98)	99.2%

[1]Includes two studies[40,41] that reported no deaths and therefore not shown in the forest plots. [2]Studies presented age-specific data using various age groups; this analysis includes studies where the age groups could be summarised as < 30 years vs ≥ 30 years **or** < 35 years vs ≥ 35 years. [3]Includes only cohorts defined by opioid injecting. [4]Includes only cohorts defined by opioid dependence or opioid use disorder. [5]Other settings include acute care (e.g. emergency departments), prisons and community settings. [6]Regions are defined as per the Global Burden of Disease (GBD) project. No studies were found for the following GBD regions: Latin America and the Caribbean; Sub-Saharan Africa; Oceania; Central Asia; Eastern Europe

Table 2: Meta-regression of potential sources of heterogeneity in the pooled all-cause crude mortality rate and standardised mortality ratio

	Crude mortality rate				Standardised mortality ratio			
	N studies	**Coefficient (SE)**	**Adj. R^2**	***P***	**N studies**	**Coefficient (SE)**	**Adj. R^2**	***P***
Cohort characteristics at baseline								
% injecting	43	4.297 (1.818)	22.67%	0.001	16	7.592 (4.725)	43.41%	0.006
% male	76	2.316 (1.745)	-0.26%	0.269	30	2.305 (2.908)	-1.89%	0.514
Mean/median age	42	1.000 (0.022)	-2.65%	0.991	19	0.953 (0.027)	10.97%	0.101
% HIV positive	23	13.569 (12.041)	27.68%	0.008	10	107.159 (270.897)	21.99%	0.102
% HCV Positive	19	4.134 (2.478)	19.73%	0.030	6	12.924 (19.898)	27.35%	0.172
% history of homelessness	8	11.081 (20.865)	7.24%	0.249	3	0.000 (0.000)	91.52%	0.160
% history of incarceration	16	0.736 (0.399)	-4.11%	0.580	6	0.674 (0.514)	-19.27%	0.632
Study characteristics								
Year of follow-up completion								
Follow-up completed by end of 1994	7	-	-	-	4	-	-	-
Follow-up continued or commenced ≥1995	90	0.851 (0.266)	-0.91%	0.606	39	1.058 (0.384)	-2.55%	0.878
Sample size	95	1.000 (0.000)	-0.19%	0.391	41	1.000 (0.000)	7.74%	0.051
Person-years of follow-up	96	1.000 (0.000)	0.66%	0.249	39	1.000 (0.000)	6.43%	0.074
Recruitment setting								
Drug treatment or harm reduction setting	57	-	-	-	29	-	-	-
Other settings[1]	40	-0.023 (0.167)	-1.25%	0.891	14	0.927 (0.209)	-2.27%	0.737

[1]*Other settings include acute care (e.g. emergency departments), prisons and community settings*

Table 3: Pooled all-cause and cause-specific CMRs among people using extra-medical opioids, pooled CMR ratios comparing men and women, and older and younger people, and pooled all-cause and cause-specific SMRs

	CMR			CMR ratio (men/women)			CMR ratio (older/younger)			SMR		
	N cohorts	**Pooled CMR (95% CI)**	**I^2**	**N cohorts**	**Pooled CMR ratio (95% CI)**	**I^2**	**N cohorts**	**Pooled CMR ratio (95% CI)**	**I^2**	**N cohorts**	**Pooled SMR (95%CI)**	**I^2**
All-cause	99	1.59 (1.40-1.80)	99.7%	45	1.38 (1.30, 1.47)	84.0%	10	1.98 (1.59, 2.47)	97.5%	43	10.03 (7.64-13.17)	99.9%
Drug-related	56	0.52 (0.46-0.59)	98.3%	15	1.44 (1.27, 1.64)	71.4%	8	1.19 (0.94, 1.50)	87.6%	12	58.43 (38.09-89.64)	99.7%
Opioid poisoning	6	0.56 (0.34-0.94)	99.3%	0	-	-	1	2.84 (2.50, 3.23)	-	1	43.50 (41.40-45.80)	-
Drug poisoning	30	0.44 (0.36-0.53)	97.7%	7	1.70 (1.34, 2.16)	31.3%	4	0.94 (0.48, 1.84)	85.5%	6	63.33 (31.31-128.08)	98.4%
Poisoning and disorders due to psychoactive substance use	28	0.50 (0.43-0.59)	98.3%	9	1.39 (1.20, 1.61)	80.3%	4	1.31 (1.02, 1.69)	91.1%	6	60.42 (31.81-114.76)	99.8%
Suicide	36	0.12 (0.10-0.16)	96.1%	10	1.78 (1.42, 2.24)	30.3%	4	1.57 (1.14, 2.17)	63.0%	10	7.93 (5.69-11.04)	97.1%
Accidental injury	29	0.14 (0.10-0.18)	97.4%	7	1.82 (1.61, 2.07)	0.0%	1	0.99 (0.65, 1.51)	-	8	6.85 (4.41-10.64)	98.2%
Violence	19	0.03 (0.02-0.03)	70.8%	4	1.68 (0.76, 3.72)	66.8%	3	1.15 (0.65, 2.05)	64.9%	8	9.75 (6.60-14.39)	81.8%
AIDS-related	36	0.19 (0.12-0.28)	99.3%	7	1.35 (0.70, 2.60)	97.1%	1	2.31 (0.47, 11.44)	-	5	18.50 (8.15-41.99)	99.1%
Liver	33	0.14 (0.08-0.27)	99.8%	6	1.69 (1.38, 2.07)	8.5%	3	8.00 (6.45, 9.92)	0.0%	11	8.60 (6.13-12.07)	96.4%
Viral hepatitis	7	0.13 (0.01-1.10)	99.9%	3	1.42 (0.80, 2.54)	65.5%	0	-	-	4	35.94 (16.06-80.42)	98.3%
Digestive diseases	13	0.06 (0.04-0.10)	97.7%	2	1.43 (0.77, 2.68)	66.5%	2	7.94 (6.38, 9.87)	0.0%	7	7.00 (4.45-11.00)	96.2%
Liver-related	20	0.16 (0.08-0.35)	99.8%	5	1.63 (1.29, 2.07)	20.5%	3	8.64 (6.79, 11.00)	0.0%	6	6.58 (3.62-11.95)	98.6%
Cardiovascular	30	0.14 (0.10-0.19)	99.1%	7	0.95 (0.87, 1.03)	1.7%	3	7.82 (4.06, 15.08)	83.2%	6	4.45 (2.97-6.66)	97.8%
Cancer	31	0.12 (0.08-0.18)	99.3%	6	1.03 (0.79, 1.34)	55.0%	3	11.51 (4.71, 28.13)	86.9%	8	2.69 (1.84-3.92)	97.8%
Respiratory	24	0.08 (0.06-0.12)	98.1%	3	0.65 (0.58, 0.73)	0.0%	2	14.09 (3.05, 65.13)	92.8%	5	10.59 (7.79-14.38)	61.8%

Figure 1: PRISMA flow diagram of studies of mortality in people using extra-medical opioids

Figure 2: Distribution of causes of death in cohorts of people using extra-medical opioids (n=19 cohorts)